REMARKS

Status of the Application and Claim Amendments

Claims 20-24, 27-30, 33, and 49-61 are currently pending. Only claims 49-61 are currently being examined, while the Office withdrew claims 20-24, 27-30, and 33 from consideration due to a Restriction Requirement.

Applicants propose a few simple claim amendments under 37 C.F.R. § 1.116 to make the grammatical structure of the pending claims even more uniform, to remove redundant words from a few claims, to change the phrase "at least" to "more than" before certain recited stability percentages in claim 49 and other claims, and to add the word "stable" to the preamble of claim 49. Those amendments do not add new matter and do not require any further search of the art. Because it is not necessary to repeat the word "thrombin" before "preparation" in the various dependent claims, Applicants have removed the redundant word "thromin." Applicants also change the article "a" appearing in a few locations in claim 49 with "at least one" to emphasize that when the article "a" or "the" appears, it should be interpreted to mean one or more than one of the modified item. Applicants change "at least" to "more than" as discussed below, to provide even better literal, word-for-word correspondence between the claims and the application text. The concept of a "stable" thrombin preparation, for example, is discussed throughout the text of the application where maintaining the activity of thrombin in the solution after long storage times is emphasized. Further, the fact that the preparations are "stable" is inherent in the limitations reciting that the thrombin maintains a certain level of activity after particular periods of time.

Hence, the amendments should allow for immediate action and Applicants respectfully request their entry. Applicants also note that the amendments would place this application in better form for appeal, should that be necessary.

Continued Request for Rejoinder of Withdrawn Claims

All of the withdrawn claims 20-24, 27-30, and 33 relate to processes of making or using the thrombin preparations of elected claims 49-61. All of the withdrawn claims also depend from elected independent claim 49. Therefore, Applicants may re-join all of the withdrawn claims as a matter of right once claims 49-61 are deemed allowable. M.P.E.P. § 821.04. Accordingly, Applicants continue to request the re-joinder of claims 20-24, 27-30, and 33.

The Claims Have Written Description Support

The Office continues to insist that claims 49-61 lack support in the application as filed under 35 U.S.C. § 112, first paragraph. (Office Action at pages 2-3.) Applicants traverse that rejection.

Again, literal, word-for-word, support is not necessary under 35 U.S.C. § 112. Instead, the specification may implicitly or inherently support the claims. M.P.E.P. § 2163.02. The application does not even have to describe a claim limitation in words to support that limitation under § 112, first paragraph. For example, figures, tables, diagrams, and the like may depict particular claimed features or may indicate inherent properties of the claimed invention. *Id.*; *and see, e.g., Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC,* 72 U.S.P.Q.2d 1190, 1199 (Fed. Cir. 2004) (a claim element reciting that the thickness of one part of a structure was wider than another part of the structure was

sufficiently supported in the application because the relative widths in question could be seen from one of the figures, though they were not described in words). Moreover, one or more species support claims to a genus, for instance, when one of ordinary skill would expect the various other members of the genus could be used in the same general way or would operate in the same general fashion. *See* M.P.E.P. § 2163.05(I)(section entitled: Addition of a Generic Claim). It is not necessary to spell-out all members of a claimed genus.

But here, the application actually provides literal or nearly literal, word-for-word support for many if not most of the claim terms that the Office objects to. All of the phrases at issue are also supported by the data tables and working examples at pages 12-15.

1. "at least 70%" and "at least 80%"

The Office states that "the support the specification teaches" at page 3, first full paragraph, "are for ranges 70-80%," and that this "does not support 'at least 70%,'" as claims 49 and 52 recite prior to the entry of the present amendments. (Office Action at pages 2-3.) The Office similarly objects to the "at least 80%" recited in dependent claims 50 and 53 prior to entry of the amendments herein. (*Id.*)

Applicants respectfully ask the Office to look again at the first full paragraph on page 3 of the specification. What it actually states is that the thrombin stability, after 12 months or more, should be "over 70-80% of the initial level" – in other words -- more than the range of 70% to 80% -- not exactly equal to that range as the Office suggests. In addition, Applicants direct the Office to page 6, second full paragraph, which states: "It is possible via the process of the invention to produce thrombin preparations which

can be stored in the liquid and/or frozen state for months or years and whose activity does not fall below 70-80% in this period." A stability that does not fall below the range of 70% to 80% is the same thing as one that remains between 70-100% or between 80-100% - in other words: one that remains at least 70% or at least 80%. Hence, contrary to the Office's position, the "at least 70%" and "at least 80%" ranges are literally supported in the application.

Even further, the instant data table at page 15 further supports the "at least 70% or 80%" range. For example, the reported stability values for two example preparations according to the invention after storage at the claimed temperature range are 100.9% and 90.6% after 12 months, and 90.1% and 82.4% after 24 months. (See the application at page 15, preparations 8 and 9.) In contrast, the other tested preparations 1-7 and 10-12 do not show even 70% stability after 12 months. (*See Id.*) Those data clearly show Applicants' possession and reduction to practice of the claimed stability ranges.

In fact, only for the sake of argument, if one takes the Office's position that only the 70-80% range itself is supported, the resulting claims would not read on Applicants' working examples! That absurd result illustrates that the Office's interpretation of the text of the application must be incorrect.

Nevertheless, to even further correlate the pending claims with the literal language used in the text at page 3 of the application, Applicants propose to replace "at least" with "more than" before the 70% and 80% figures in the claims.

2. "At least 90%"

The data in the application expressly supports a stability of "at least 90%" after 12 or 24 months of storage at 20-25 °C, as presented in dependent claims 51 and 54. (Office Action at page 3.) For instance, the stability values of two exemplary preparations according to the invention, after storage at the claimed temperature range, are 100.9% and 90.6% after 12 months. Thus, those two examples are "at least 90%" stable after 12 months. (See the application at page 15, preparations 8 and 9.) Further, one of the two preparations has a thrombin activity of 90.1% after 24 months, and thus is certainly "at least 90%" stable after 24 months. (See *Id.*) Hence, the application expressly teaches preparations that retain "at least 90%" stability after the stated time periods, and at the stated temperatures.

In any event, Applicants propose to amend the words "at least" to "more than" herein, both for consistency with the changes made to claims 49 and 50 reciting lower percentages, and for even better correlation to the figures presented in the tables at page 15.

Applicants further note that specific numerical ranges may also be inherently supported by data in an application. For example, in the case of *In re Wertheim*, working examples showing 36% and 50% of a particular ingredient within a claimed composition, coupled with a written disclosure of a range of 25% to 60%, was found sufficient to support a claimed range of 35% to 60%. M.P.E.P. § 2163.06(III); 191 U.S.P.Q. 90, 93-97 (C.C.P.A. 1976). In other words, disclosure of a value of 35%, approximating the claimed end point of 36% was sufficient support for the claim. Similarly here, particular examples of the claimed preparations that retain 90.1% or

90.6% or 100.9% of their original stability after the claimed time periods and at the claimed temperature range also inherently support claims drawn to a range of "at least 90%" or "more than 90%."

Finally, those three values in the tables at pages 12-15 stand out in comparison the other data because they derive from the only exemplary preparations that contain all of the ingredients required by claim 49. Hence, one of ordinary skill in the art would certainly recognize that Applicants possessed and clearly disclosed the features of claims 51 and 54.

3. "Sugar alcohol at a maximum of 2%"

The Office objects to the requirement in claim 58 for "sugar alcohol at a maximum of 2%" because, in the Office's opinion, referring to Table 4 at page 12, the application supports only mannitol at that concentration range. (Office Action at page 3.) Applicants submit that the standard the Office is applying here is far too high.

In this case, the use of mannitol in Table 4, coupled with the remaining disclosure, directs those of ordinary skill in the art that the concentration range which works for mannitol could be used with sugar alcohols generally, for example, glycerol. It is clear from the remaining text of the application that other sugar alcohols could be substituted for mannitol. (*See, e.g.,* original claim 8 generally reciting "sugar alcohols.")

Further, the M.P.E.P. explains that an example species supports claims to a genus so long as the behavior of other members of the genus is reasonably predictable based on that of the disclosed species. *See* M.P.E.P. § 2163.05(I)(section entitled: Addition of a Generic Claim). Here, the Office has provided no evidence to suggest that there is anything unique about mannitol and that other sugar alcohols would not behave

similarly. Hence, Applicants submit that the Office's rejection of claim 58 must be in error. The working examples and remaining original disclosure more than adequately support claim 58.

4. Time Ranges

It is not clear to Applicants whether the Office also intended to reject the application over the "at least 12 months" and "at least 24 months" in claims 49-54. The Office appears to object to any phrase preceded by "at least," but only specifically comments about the claimed thrombin activity values. (See the Office Action at pages 2-3.) Thus, if the Office intended to reject the "at least 12 or 24 months" phrases as well, it has not made a *prima facie* case because it has not provided information to help Applicants or a reviewing body such as the Board of Patent Appeals and Interferences understand the basis for the rejection. *See In re Zurko,* 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001); *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

Nonetheless, and solely to speed prosecution, Applicants note that those time ranges are specifically and literally presented in the tables at pages 13-15, and again at page 3, first full paragraph, and page 6, last incomplete paragraph. Therefore, the application text supports those time ranges word-for-word.

In light of all of the above remarks, Applicants respectfully request the Office to enter the claim amendments herein and to withdraw all of the rejections under 35 U.S.C. § 112, first paragraph.

The Claims Are Nonobvious

The Office also continues to assert that claims 49-58 are obvious over Lorne or Allary taken with Hanada, Brezniak, and Altshuler, and now extends that rejection to

claims 59-61. (Office Action at pages 3-6; Lorne et al. *Rev. Fr. Transfus. Hemobiol.* 32: 391-400 (1989); Allary et al. *Ann. Pharmaceutiques Francaises* 48: 129-35 (1990); United States Patent No. 5,945,103 to Hanada et al.; Brezniak et al., *Blood Coag. and Fibrinolys.* 5: 847-8 (1994); and United States Patent No. 4,363,319 to Altshuler.) Applicants also traverse that rejection.

Again, a *prima facie* case of obviousness must meet the following three requirements: (1) all of the claim limitations must be taught or suggested; (2) there must be an objective teaching in the prior art, and not in the applicant's disclosure, to combine or modify the art; and (3) the prior art must teach a reasonable expectation of success in performing that combination or modification. (*See* M.P.E.P. §§ 2141-2143.) This rejection does not meet any of the above requirements. Thus, it is not a *prima facie* case.

The Cited Documents Do Not Teach All of the Claim Limitations

First, none of the cited literature above actually teaches the long-term stability properties of claim 49. Instead, the Office contends, without providing substantial evidence, that such stability properties are nevertheless inherent in the five cited publications. (Office Action at page 5, first paragraph.)

The Office here concludes that the cited art inherently would meet all of the functional limitations of Applicants' claims. But the Office provides no reasoning or evidence to support that proposition, as is required to make a *prima facie* case. *In re Zurko,* 59 U.S.P.Q.2d 1693; *In re Lee*, 61 U.S.P.Q.2d 1430.

Moreover, a prior art reference may be used to support an obviousness rejection only for what it objectively teaches to those of ordinary skill. It is incorrect to base

obviousness rejections on inherent properties unless those properties are actually taught or suggested in the art itself when that art is taken as a whole. *See* M.P.E.P. § 2143.03. As the courts have long explained, obviousness must be based only on properties that are actually known before the application is filed. But inherent properties, by definition, are usually unknown. Something that is unknown cannot be obvious. *See In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 757 (C.C.P.A. 1977), citing *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).

Therefore, any obviousness rejection that is improperly based on an unknown and un-taught inherent property is not a *prima facie* case and must be withdrawn.

That is the case here, because none of the five cited publications taken alone or in combination suggests that a thrombin preparation could be made more than 70% stable for over 12 or even 24 months at 20-25 °C using the specific set of ingredients claimed here. In addition, none of the five publications suggests that one could achieve the heightened stability recited in claims 50-54 using the materials claimed. Nor do any of the publications suggest that it is possible to achieve the claimed levels of stability while at the same time preventing a viscosity increase as taught by claim 59, for example.

Due to those defects, the cited combination does not objectively teach or suggest all of Applicants' claim limitations, and thus fails the first requirement of a *prima facie* case of obviousness.

There is No Motivation to Combine the Cited Publications

The cited combination also fails the second requirement: motivation to combine the teachings of the cited art.

In order to find a motivation to combine publications, there must be an objective suggestion or desire within the prior art itself to make the necessary modifications. *See, e.g., Winner Int'l. Realty Corp. v. Wang,* 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000). Even if a modification is theoretically possible or even if the general ingredients necessary are readily available, the prior art must still set forth an objective wish or desire for the specific changes embodied by the claims. *See* M.P.E.P. § 2143.01; *and see In re Gordon,* 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). For instance, a combination showing only that the claimed composition is one of many possibilities or trade-offs is not sufficient. *See Winner v. Wang*, 53 U.S.P.Q.2d 1580; *and see* M.P.E.P. § 2143.01. Instead, as the Federal Circuit has repeatedly explained, "particular findings must be made as to why one of ordinary skill in the art, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Lee,* 61 U.S.P.Q.2d at 1433 (quoting *In re Kotzab,* 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

Here, the Office cites a collection of different papers which, in combination, would actually push one of ordinary skill in a different direction from the claims. Applicants' claim 49, for example, requires a preparation having a specific minimum level of thrombin activity after a particular period of storage, and which comprises a noncovalently binding inhibitor of thrombin activity, at least one soluble calcium salt, sodium chloride, at least one buffer substance and at least one other ingredient chosen from a specific list. Compared to those claimed ingredients and properties, three of the documents the Office cites actually direct those of ordinary skill away from using

noncovalent inhibitors of thrombin activity for thrombin storage. The other two publications make no mention of such inhibitors.

At best, the five articles merely show that different ingredients used in Applicants' claimed preparations were available to those of ordinary skill in the art at the time of this invention, but they do not demonstrate any particular desire to select the specific set of ingredients Applicants choose. And certainly, the set of articles does not suggest that by selecting the particular ingredients that Applicants claim, one would be able to keep thrombin stable over the long periods of time at high temperatures according to the instant claims.

Thus, the instant combination also fails to meet the second requirement for a *prima facie* case.

There is No Expectation of Success

Third, the five cited publications do not suggest that one should store thrombin solutions for the long term in the specific set of ingredients claimed here. Hence, those publications, in light of the prior art as a whole, provide no reasonable expectation that thrombin would retain more than 70% of its activity when stored in Applicants' claimed solutions, let alone more than 80% or more than 90%.

Further, in considering claim 59, for example, the art prior to Applicants' invention taught that in order to achieve a thrombin preparation that is stable over the long term, that preparation should be stored in a viscous solution with high concentrations of polyols such as, for example, 10% or more of glycerol. (See the specification at page 3, first full paragraph, lines 11-14.)

For instance, Altshuler teaches solutions with 30% glycerol or 15% mannitol and/or another highly viscous additive such as polyethylene glycol. (*See* Altshuler at col. 6, Examples I and II, and col. 8, line 64, to col. 9, line 2.) But even those solutions may not be stable beyond 8 months at 22 °C. (*Id.* at col. 9, lines 28-37.) European Patent Publication No. 0 221 700 A2 also teaches using 25% (w/w) glycerol or other "high concentrations of polyols" to stabilize thrombin preparations. (*See Id.* at page 1, line 26, and pages 4-5, Tables III and IV.) Some of the resulting preparations lost 29% of their activity within the first 41 days at 25 °C.

Claim 59, in contrast, requires that the concentration of the additives is low enough (e.g. 1-2% polyol) such that those ingredients do not increase the viscosity of the preparation. Yet, at the same time, the preparation of claim 59 is required to retain more than 70% of its original thrombin activity at essentially room temperatures over a period of at least one year. The art on thrombin preparations, as shown above, does not suggest that such a result would be feasible.

Thus, in summary, the Office has not supported this rejection with the appropriate level of substantial evidence or fact-based reasoning to make a *prima facie* case. *In re Zurko,* 59 U.S.P.Q.2d 1693; *In re Lee*, 61 U.S.P.Q.2d 14. Accordingly, the rejection fails all three parts of the test for a *prima facie* case of obviousness, and Applicants request its withdrawal.

Conclusion

In light of the remarks and amendments above, Applicants submit that this application is in condition for allowance. Accordingly, Applicants request the entry of

this Reply under 37 C.F.R. § 1.116, the allowance of claims 49-61, and the re-joinder and allowance of claims 20-24, 27-30, and 33.

Please grant any extensions of time required to enter this Reply. Please also charge any fees necessary to enter this Reply that are not otherwise found herewith to deposit account 06-0916.

Respectfully submitted,

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Dated: June 12, 2006

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